HYPERTENSION: SEVEN DECADES OF TREATMENT*

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IN 1628 William Harvey proved that the blood circulated in vascular channels. In 1733 Stephen Hales proved that the blood circulates because it is under pressure. In 1880 Samuel von Basch introduced a method for the bloodless measurement of blood pressure.

These crucial observations led inevitably to the recognition and definition of human hypertensive disease. In the past seven decades innumerable investigations have probed its clinical manifestations, anatomical alterations, chemical, physiological, and psychological concomitants. It can be assumed that these investigations had a common goal: the prevention and cure of hypertensive disease. Along the way there has been some small therapeutic success in coarctation of the aorta, unilateral renal vascular disease, pheochromocytoma, and aldosteronism. However, the prevention and cure of essential hypertension are as elusive as ever and the possibility of clinical control of the disease is still on trial even though, in regard to control, general opinion is heavily in the affirmative.

The first documented attempt at treatment for hypertension was reported in 1899 by Henri Huchard, who suggested elimination of dietary protein, especially meat and fish, on the assumption that intestinal autointoxication was the culprit.

The next definitive therapeutic suggestion was offered by Leon Ambard and A. Beaujard in 1904 in the form of salt restriction. They mistakenly implicated the chloride ion but did demonstrate reduction of blood pressure in hypertensive patients on restricted salt intake, the cases being documented with charted data. There was little acceptance of salt restriction in this country until the method was revived by Allen and Sherrill in 1922. By 1940 it was largely abandoned again

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because of general failure to confirm a beneficial effect. A second revival of the salt-restricted diet occurred in 1944, when Kempner's rice diet was popular. Contrary to Walter Kempner's opinion, the claimed beneficial effect on blood pressure was ascribed to the restriction of salt and not of protein. Although the rice diet has lost favor, many physicians still consider sodium restriction to be effective in reducing blood pressure. This belief is supported by the statement that antihypertensive drugs are more effective when administered with a thiazide. Although restriction of sodium alone is widely applied, its effectiveness in producing a significant decrease in blood pressure has not been documented with any degree of certainty.

For the record I shall mention without comment several exotic agents used at times during the past several decades: extract of garlic, methylene blue, watermelon seeds, and vitamin A.

Among the earlier drugs, thiocyanate was popular for several years. Originally suggested by W. Pauli in 1903, it was widely used in the 1930's and discarded when it became apparent to all investigators that thiocyanate was capable of producing severe neurological intoxication and was only occasionally effective in lowering blood pressure. Sodium nitroprusside, which slowly liberates thiocyanate, was used for a short period and eventually discarded because of toxicity and uncertain effectiveness.

Sympathectomy appears to have been suggested for the first time in 1923, in Germany. It was introduced into this country by Alfred W. Adson, Max M. Peet, G. Heuer, K. Grimson, William Hinton, and others. It was Reginald H. Smithwick who established the operation worldwide as the most effective treatment available at that time. This opinion was attested to by an extensive literature between 1939 and 1949, extolling the statistical improvement in morbidity and mortality after the operation. There was very little dissent in the literature; praise for sympathectomy was often extravagant.

About 1950 antihypertensive drugs became popular, and interest in sympathectomy faded, quite suddenly. Not until the advent of these pharmacological agents were physicians impressed by the fact that the results of sympathectomy did not justify the early predictions.

Bilateral adrenalectomy should be mentioned in passing for its historical interest only. This procedure was introduced with as much

enthusiasm as the many other forms of treatment which were eventually discarded as ineffective.

Acting on Bright's suggestion that hypertension was a consequence of restriction of renal blood flow due to intrinsic renal disease, L. Paunz in 1930 performed renal omentopexy in the dog. He clamped the main renal artery of the omentum-transplanted kidney and one month later removed the opposite kidney. The dogs continued in good health without azotemia and remained normotensive for 10 months, at which time they were sacrificed. Paunz demonstrated that the operated kidney, lacking a main renal artery, derived an adequate blood supply from the omental graft. This observation needed only the stimulus of Harry Goldblatt's classic experimental hypertension to suggest renal omentopexy, myopexy, and splenopexy as promising treatments for hypertension. However in 1939 J. S. Mansfield was unable to reduce the blood pressure in experimental hypertensive dogs with this operation and in 1940 M. Bruger and R. F. Carter reported failure of renal-omentopexy to reduce blood pressure in man. We and others have confirmed the ineffectiveness of the "pexy procedures" in man.

Goldblatt's demonstration opened another avenue for therapeutic investigation. In 1935 Krebs showed that deamination requires the presence of oxygen. It was postulated that local ischemia would prevent renal participation in deamination, allowing pressor amines to enter the circulation. In 1941 J. Bing and M. B. Zucker presented evidence in the cat to support this possibility. In 1942 K. A. Oster showed that pressor amines are inactivated by some quinone precursors. These substances were administered to hypertensive rats by B. Friedman and his associates in 1942 and significant reduction of blood pressure was reported. Such evidence, obtained from the unreliable rat, did not seem to warrant a trial in hypertensive man. At this same time, motivated by the "failure of deamination" theory, H. Schroeder and M. H. Adams proposed the administration of tyrosinase, a phenolic aminase obtained from mushrooms. They demonstrated appreciable reduction of blood pressure in hypertensive rats and dogs. Tyrosinase was promptly administered to hypertensive man and the antihypertensive effect was confirmed by several investigators. However, the reduction in blood pressure was shown to be just as great when heat-inactivated tyrosinase was used, indicating a nonspecific pyrogenic reaction, not a specific enzyme. Accordingly this hypothesis lost favor

as did the proposed therapies dependent on it, such as the administration of vitamin A and methylene blue in addition to quinone precursors and aminoxidases.

Goldblatt's experiment continued to have a profound influence on the direction of therapy in the 1940's. His observation, widely confirmed, that unilateral constriction of the renal artery did not produce persistent hypertension led to the assumption that the normal unclamped kidney produces an inhibitor substance. In 1943 I. H. Page and his associates took the next reasonable step. They prepared an extract of normal kidney and administered it parentally to hypertensive animals and man. The reduction in blood pressure was striking. However, as with tyrosinase, this effect on blood pressure was shown by other investigators to be the result of a nonspecific pyrogenic reaction. Heat-inactivated kidney extract was just as effective as unheated extract. Similar reduction in blood pressure was accomplished with nonspecific pyrogenic substances such as mold and typhoid vaccine.

To the list of proposed treatments for hypertension we should add prefrontal lobotomy—long since discarded—and radio-frequency carotid sinus stimulation, which is now being investigated.

Before discussing the present-day drug therapy may I quote a little gem composed by Ed Weiss in 1937 when enthusiasm for sympathectomy was gaining momentum:

> Now what is done to this poor fellow in an effort to "bring his pressure down?" Because of an ill-founded idea that protein is responsible for hypertension and kidney disease he is denied meat and eggs, especially red meat, which for some reason is looked upon with particular dread. Then his diet is rendered even more unpalatable by the withdrawal of salt. One would sympathize with this half-starved fellow except that he probably would not be able to eat anyway, his teeth having been removed on the theory that focal infection has something to do with hypertension. Even before this he had sacrificed his tonsils and had had his sinuses punctured because of the same theory. In case some food had been consumed the slight colonic residue was promptly washed out by numerous "colonic irrigations," especially during the period when the theory of auto-intoxication was enjoying a wave of popularity. To add to his unhappiness he may be told to stop work and exercise and of course, is denied alcohol and tobacco as well as coffee and tea. And

now to cap the climax of his difficulties the unfortunate person with hypertension seems about to fall into the clutches of the neurosurgeon who is prepared to separate him from his sympathetic nervous system.

Several years later Homer Smith was asked to express an opinion on the rationale of current therapies for hypertension. He substituted "investigation and desperation" for sympathectomy and "deprivation" for the rice diet. In retrospect it would seem that, with humor and conviction, Ed Weiss and Homer Smith were true prophets.

Now a final word on current drug therapy 70 years after the first definitive suggestion for treatment by Henri Huchard.

It should be permissible to take some liberties in this part of the discussion since I shall express a minority opinion. This opinion is shared by Herbert Chasis, hence I am assured of at least one sympathetic listener. The following excerpt is from an editorial which we wrote in 1965; we see no reason for changing our views in 1969:

> Our attitude is one of skepticism and restraint in accepting blood pressure lowering drugs as even a partial answer to the management of hypertensive disease. Our view is neither nihilistic in that we deny all forms of therapy in hypertension since it is established that unilateral nephrectomy or renal artery reconstruction in some patients can be curative, nor purist in that we demand discovery of the cause of essential hypertension before accepting a therapy as being empirically beneficial. A drug that will maintain blood pressure in the normal range in the supine as well as in the upright position without adverse physiological effects for all 24 hours over a period of years, when and if available, may well make medical history. As [M. D.] Sheps and [A.] Shapiro say in a recent paper. "It is not therapeutic nihilism to demand proof of efficacy of a new drug, for with increased therapeutic potential have come increased therapeutic risks." We may add to this admonition a responsibility to the very disease under consideration, since complacency and acceptance of present day drug therapy could lead to the stifling of sadly needed basic approaches to the problems of hypertensive disease. We find support for this unhappy circumstance in the world medical literature of studies concerned with hypertension. From 1938-1943, 85%-90% of all published studies dealt with basic observations directed toward etiology and patho-

genesis; from 1943-1950 with the advent of surgical sympathectomy, basic research decreased to 62% of the total published studies; concomitantly with the flood of papers dealing with the administration of antihypertensive drugs basic studies decreased to 47% of the total. One needs only to look back at the past 70 years to be . . . deeply concerned at the worldwide enthusiasm generated by many proposed therapies for hypertension which eventually met . . . well deserved . . . oblivion. Current enthusiasm generously supported by the persuasive influence of pharmaceutical manufacturers, for the widespread use of antihypertensive drugs, is an example in point. After about 15 years of assorted data collecting, we believe that the alleged usefulness of antihypertensive drugs rests on conclusions drawn from notoriously uncertain statistical compilations compounded by equally uncertain estimate of morbidity and mortality in the natural history of a disease of highly unpredictable course. If the combined efforts of all those involved in this clinical maneuver had been applied to demonstrating without doubt that arteriolar and arterial disease are in fact a consequence of simple elevation of blood pressure, even the writers of this statement would be eager beavers on the antihypertensive drug band-wagon. In spite of present lack of convincing data such an outcome is not wholly inconceivable, in view of some bits of presumptive evidence favoring this opinion and of the eminence and skill of many who have been diverted from basic thinking in this problem.

This editorial statement was not meant to deny categorically the possible clinical usefulness of antihypertensive agents. However it does express the concern that the present era of empirical treatment for hypertension may still prove to be an era of uncontrolled clinical-pharmacological experiment rather than one of lasting benefit to the hypertensive patient.

This minority opinion rests largely on the fact that drug therapy can be pursued seriously only by those who believe that cardiac, cerebral, retinal, and renal vascular disease is a direct consequence of elevated blood pressure. However there are alternate possibilities: vascular disease and hypertension may stem from a common cause and represent different manifestations of the same disorder; vascular disease may arise independently, the association with hypertension being

coincidental; vascular disease may precede and account for the hypertension; and finally, hypertension, arising independently, may accelerate the progress of prior vascular disease. At this time, it is impossible to establish the validity of any of these theories. Therefore it seems hazardous to accept without some skepticism the critical foundation on which drug therapy is based. We intend simply to emphasize the need for proof, more convincing than statistical data, for the clinical value of antihypertensive drug therapy. It is unfortunate that acceptable techniques for obtaining the necessary proof are not now available.

Listing of therapies which have been suggested over a period of seven decades serves to emphasize the evolution and great diversity of approaches to the prevention, control, or cure of essential hypertension: protein restriction, salt restriction, extract of garlic, methylene blue, watermelon seed, vitamin A, thiocyanate, sympathectomy, renal "Pexy Procedures," tyrosinase, quinone precursors, adrenalectomy, renal extract, prefrontal lobotomy, radio-frequency carotid-sinus stimulation, and antihypertensive drugs.

Of the methods listed only two types of therapy have persisited: antihypertensive drugs and salt restriction.

Antihypertensive drugs are last on the list and, at least for chronological reasons, have become the current accepted treatment. If we dare be guided by history it should be permissible to wonder if they too are waiting to be replaced by a therapy of greater promise. And in the absence of more definitive information as to the effectiveness of sodium restriction it should be permissible to take this suggestion with a grain of salt.

Conclusion

Excluding the few potentially curable forms, it would seem that current treatment of hypertension is, at best, in a tentative state. Indeed, one form of current therapy, sodium restriction, has taken us full circle, back to 1904. It may be said that, like generals, treatments for hypertension do not die, they fade away when a new and more promising therapy appears. Protein restriction gave way to salt restriction, which in turn lost favor with the advent of sympathectomy. Even that formidable therapy could not withstand the onslaught of current antihypertensive drugs. The disturbing fact is clear that each discarded treatment was introduced with optimism and enthusiasm even though, in

the absence of definitive information on etiology and pathogenesis, reliance was placed entirely on statistical data in a highly variable disease. The failure of so many proposed therapies brings to mind Armand Trousseau's comment: "always use a therapeutic agent when it is new and still has the power to cure."

In view of all that has been said about the current treatments for hypertension, some of which are in favor and some are still in doubt, there is no need to labor the point that this form of therapy is still on trial. I expect no serious contradiction, even from those most enthusiastic, to the belief that current drug therapy is not the final answer to the control of high blood pressure and its accompanying vascular disease.

Etiology and pathogenesis have eluded two generations of investigators. The conclusion is inescapable that new approaches to this problem are desperately needed.

Perhaps solution of the problem should be subjected to the same radical and sweeping changes that are currently being forced on institutions of learning. Admitting the hazards inherent in sudden change of direction, in most instances initiated by immature and untrained minds, we must recognize that some good should result, if only from stimulation of new thinking among members of the older generation. The analogy is clear. The problem of hypertension requires new, full-time, determined, properly motivated basic and clinical scientists who will scan the past for all useful information in order to detect a new line of departure which promises greater success than has been achieved during the past 70 years. Implementation of such a program for the future is beyond the scope of this presentation. I believe that it has merit if only to shake the hypertension problem out of its present complacency.

It is the hope of the New York Heart Association that this conference may serve in some degree to divert research on hypertension into either new or as yet inadequately explored directions.